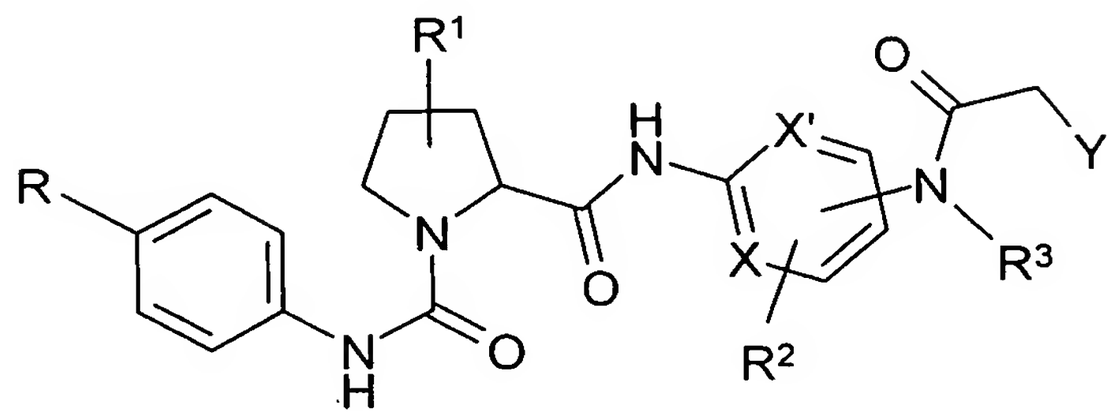
Patent Claims

1. Compounds of the formula I



I

in which

R		denotes Hal, -C≡C-H, -C≡C-A or OA,
R^1		denotes H, =O, Hal, A, OH, OA, A-COO-, Ph-$(CH_2)_n$-COO-, cycloalkyl-$(CH_2)_n$-COO-, A-CONH-, A-CONA-, Ph-CONA-, N_3, NH_2, NO_2, CN, COOH, COOA, $CONH_2$, CONHA, $CON(A)_2$, O-allyl, O-propargyl, O-benzyl, =N-OH, =N-OA or $=CF_2$,
X, X'		each, independently of one another, denote CH, CHal or N,
Y		denotes R^4 or Hal,
Ph		denotes phenyl which is unsubstituted or mono-, di- or trisubstituted by A, OA, OH or Hal,
R^2		denotes H, Hal or A,
R^3		denotes H or A,
R^4		denotes OH, OA, A-COO-, NHA, NHAr, NAA', Het or -NH-CHR^5-$COOR^3$,
R^5		denotes H, A, -CHR^3-OH, $(CH_2)_n$-Ph, $(CH_2)_n$-COOH, $(CH_2)_n$-$CONH_2$, $(CH_2)_p$-NH_2, $(CH_2)_n$-NH(=NH)NH_2, $(CH_2)_n$-Het^1 or $(CH_2)_n$-SR^3,
Het		denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubsti-

tuted by A, OH, OA, CN, COOH, COOA and/or carbonyl oxygen (=O),

Het^1 denotes a mono- or bicyclic aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by A, OH, OA and/or CN,

A, A' each, independently of one another, denote unbranched, branched or cyclic alkyl having 1-12 C atoms, in which, in addition, 1-7 H atoms may be replaced by F and/or chlorine,

Ar denotes naphthyl, biphenyl, or phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, OR^3, $N(R^3)_2$, NO_2, CN, $COOR^3$, $CON(R^3)_2$, NR^3COA, $NR^3CON(R^3)_2$, NR^3SO_2A, COR^3, $SO_2N(R^3)_2$, $S(O)_nA$, $-[C(R^3)_2]_n-COOR^3$ or $-O-[C(R^3)_2]_p-COOR^3$,

Hal denotes F, Cl, Br or I,

n denotes 0, 1, 2 or 3,

p denotes 1, 2, 3, 4 or 5,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

2. Compounds according to Claim 1 in which

R denotes Hal or -C≡C-H,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

3. Compounds according to Claim 1 or 2 in which

R^1 denotes H, =O, Hal, A, OH or OA,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

4. Compounds according to one or more of Claims 1-3 in which

R^1 denotes OH,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

5. Compounds according to one or more of Claims 1-4 in which

X denotes CH or N,

X' denotes CH,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

6. Compounds according to one or more of Claims 1-5 in which

R^2 denotes H or Hal,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

7. Compounds according to one or more of Claims 1-6 in which

R^3 denotes H or alkyl having 1, 2, 3, 4, 5 or 6 C atoms,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

8. Compounds according to one or more of Claims 1-7 in which

Het denotes a monocyclic saturated, unsaturated or aromatic heterocycle having 1 to 2 N and/or O atoms, which may be unsubstituted or mono-, di- or trisubstituted by A, OH and/or OA,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

9. Compounds according to one or more of Claims 1-8 in which

Het denotes furyl, thienyl, pyrrolyl, imidazolyl, pyridyl, pyrimidinyl, pyrazolyl, thiazolyl, indolyl, pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl, each of which is

unsubstituted or mono-, di- or trisubstituted by A, OH and/or OA,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

10. Compounds according to one or more of Claims 1-9 in which

Het^1 denotes an unsubstituted mono- or bicyclic aromatic heterocycle having 1 to 2 N, O and/or S atoms,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

11. Compounds according to one or more of Claims 1-10 in which

R^5 denotes H or A,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

12. Compounds according to one or more of Claims 1-11 in which

Ar denotes naphthyl, or phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, OR^3, $N(R^3)_2$, NO_2, CN, $COOR^3$ or $CON(R^3)_2$,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

13. Compounds according to one or more of Claims 1-12 in which

Ar denotes phenyl,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

14. Compounds according to one or more of Claims 1-13 in which

R denotes Hal or -C≡C-H,

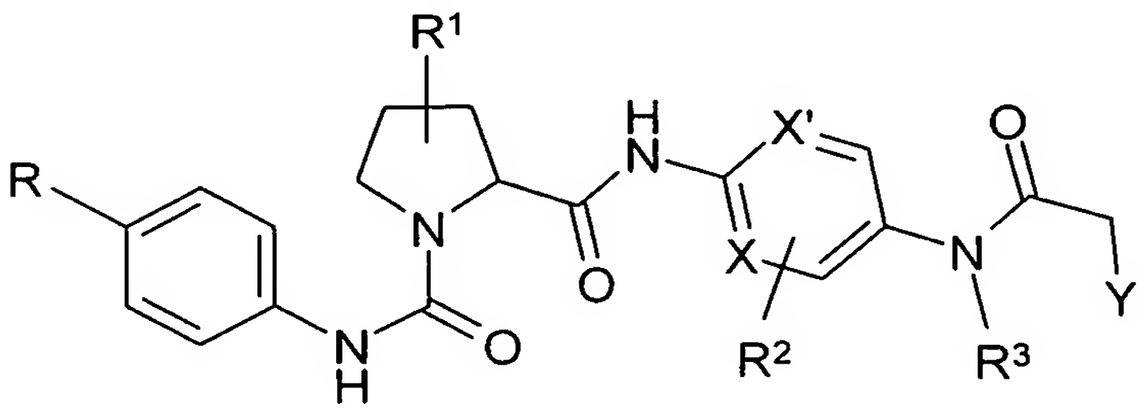
R^1 denotes OH,

X denotes CH or N,

X'	denotes CH,	
Y	denotes R^4 or Hal,	
R^2	denotes H or Hal,	
R^3	denotes alkyl having 1, 2, 3, 4, 5 or 6 C atoms,	
R^4	denotes OH, OA, A-COO-, NHA, NHAr, NAA', Het, -NH-CHR^5-COOR^3 or -NH-CHR^5-COOH,	
R^5	denotes H or A,	
Het	denotes a monocyclic saturated, unsaturated or aromatic heterocycle having 1 to 2 N and/or O atoms, which may be unsubstituted or mono-, di- or trisubstituted by A, OH and/or OA,	
A, A'	each, independently of one another, denote unbranched, branched or cyclic alkyl having 1-12 C atoms, in which, in addition, 1-7 H atoms may be replaced by F and/or chlorine,	
Hal	denotes F, Cl, Br or I,	
n	denotes 0, 1, 2 or 3,	
p	denotes 1, 2, 3, 4 or 5,	

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

15. Compounds of the formula Ia



Ia

according to one or more of Claims 1-14

in which

R denotes Hal or -C≡C-H,

R^1 denotes OH,

X denotes CH or N,

X' denotes CH,

Y denotes R^4 or Hal,

R^2 denotes H or Hal,

R^3 denotes alkyl having 1, 2, 3, 4, 5 or 6 C atoms,

R^4 denotes OH, OA, A-COO-, NHA, NAA', Het, $-NH-CHR^5-COOR^3$ or $-NH-CHR^5-COOH$,

R^5 denotes H or A,

Het denotes a monocyclic saturated, unsaturated or aromatic heterocycle having 1 to 2 N and/or O atoms, which may be unsubstituted or mono-, di- or trisubstituted by A, OH and/or OA,

A, A' each, independently of one another, denote unbranched, branched or cyclic alkyl having 1-12 C atoms, in which, in addition, 1-7 H atoms may be replaced by F and/or chlorine,

Hal denotes F, Cl, Br or I,

n denotes 0, 1, 2 or 3,

p denotes 1, 2, 3, 4 or 5,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

16. Compounds according to Claim 1 selected from the group

1-N-(4-chlorophenyl)-2-N-{4-[(2-dimethylaminoethanoyl)-methylamino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-(*N*-methyl,*N*-butylamino)-ethanoyl)methylamino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-(morpholin-4-yl)ethanoyl)methyl-amino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-(4-hydroxypiperidin-1-yl)-ethanoyl)methylamino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-di-carboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-(2,6-dimethylmorpholin-4-yl)-ethanoyl)methylamino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-di-carboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-(3-cyclohexylmethylpiperidin-1-yl)ethanoyl)methylamino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-di-carboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-diethylaminoethanoyl)methyl-amino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-(*N*-methyl,*N*-ethylamino)-ethanoyl)methylamino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-di-carboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-(2-methylimidazol-1-yl)-ethanoyl)methylamino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-di-carboxamide,

1-N-(4-ethynylphenyl)-2-N-{4-[(2-dimethylaminoethanoyl)methyl-amino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-(4-chlorophenyl)-2-N-{2-fluoro-4-[(2-dimethylamino-ethanoyl)methylamino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-di-carboxamide,

1-N-(4-chlorophenyl)-2-N-{5-[(2-dimethylaminoethanoyl)methyl-amino]pyridin-2-yl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-acetoxyethanoyl)methylamino]-phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

methyl (2R,4R)-2-[({[4-({1-[1-(4-chlorophenylcarbamoyl)-4-hydroxypyrrolidin-2-yl]methanoyl}amino)phenyl]methylcarbamoyl}-methyl)amino]-4-methylpentanoate,

1-N-(4-chlorophenyl)-2-N-{4-[(2-ethylaminoethanoyl)methyl-amino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-chloroethanoyl)methylamino]-phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-cyclohexylaminoethanoyl)-methylamino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarbox-amide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-methylaminoethanoyl)methyl-amino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-isopropylaminoethanoyl)methyl-amino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-*tert*-butylaminoethanoyl)methyl-amino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-cyclopentylaminoethanoyl)-methylamino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarbox-amide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-cyclopropylmethylamino-ethanoyl)methylamino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-di-carboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-hydroxyethanoyl)methylamino]-phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-methoxyethanoyl)methylamino]-phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-ethoxyethanoyl)methylamino]-phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-propoxyethanoyl)methyl-amino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-(4-chlorophenyl)-2-N-{4-[(2-butoxyethanoyl)methyl-amino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-(4-ethynylphenyl)-2-N-{4-[(2-methoxyethanoyl)methyl-amino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

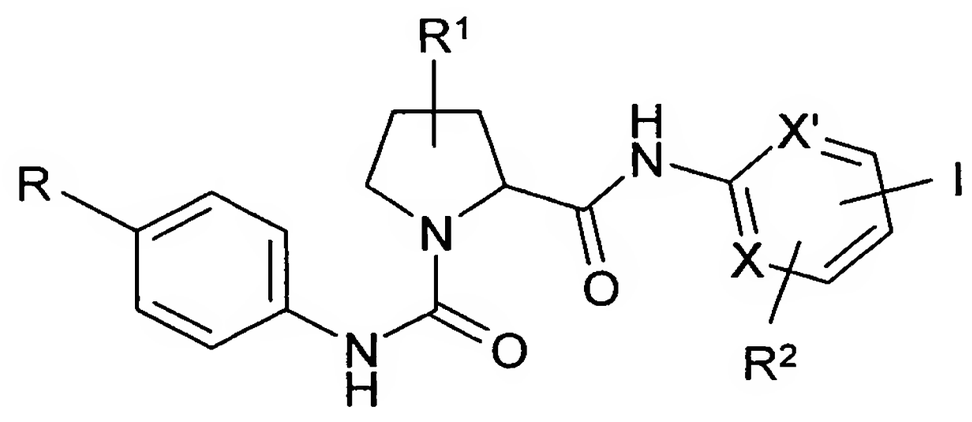
1-N-(4-chlorophenyl)-2-N-{2-fluoro-4-[(2-methoxyethanoyl)-methylamino]phenyl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarbox-amide,

1-N-(4-chlorophenyl)-2-N-{5-[(2-methoxyethanoyl)methylamino]-pyridin-2-yl}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

and pharmaceutically usable derivatives, solvates, salts and stereo-isomers thereof, including mixtures thereof in all ratios.

17. Process for the preparation of compounds of the formula I according to Claims 1-16 and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, characterised in that

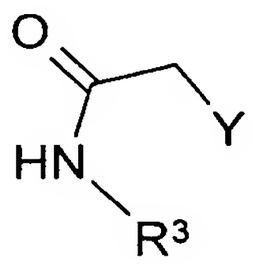
a) a compound of the formula II



II

in which R, R^1, R^2, X and X' have the meanings indicated in Claim 1,

is reacted with a compound of the formula III



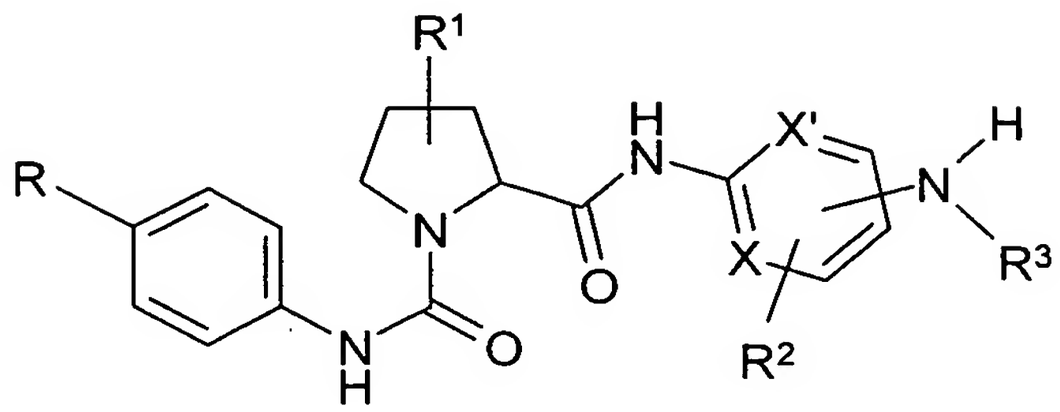
III

in which

Y and R^3 have the meanings indicated in Claim 1,

or

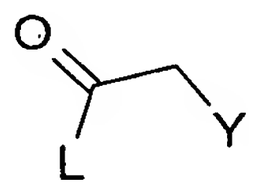
b) a compound of the formula IV



IV

in which R, R^1, R^2, R^3, X and X' have the meanings indicated in Claim 1,

is reacted with a compound of the formula V



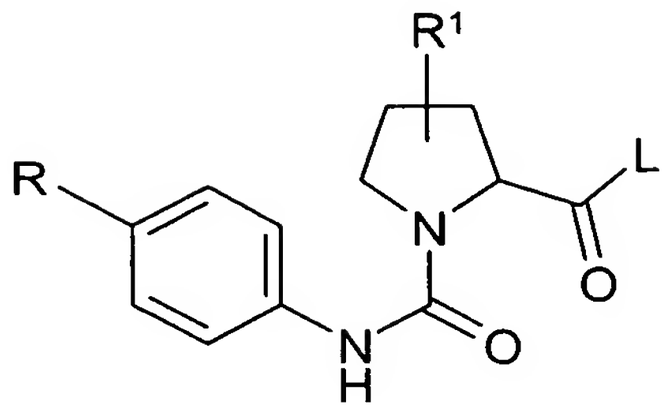
V

in which Y has the meaning indicated in Claim 1 and

L denotes Cl, Br, I or a free or reactively functionally modified OH group,

or

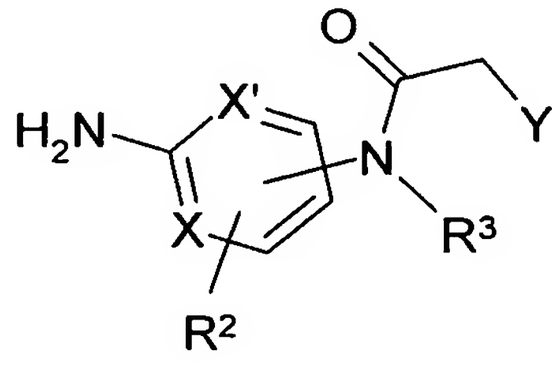
c) a compound of the formula VI



VI

in which R and R^1 have the meanings indicated in Claim 1,
and
L denotes Cl, Br, I or a free or reactively functionally modified OH group,

is reacted with a compound of the formula VII



VII

in which R^2, R^3, X, X' and Y have the meanings indicated in Claim 1,
and/or
a base or acid of the formula I is converted into one of its salts.

18. Compounds of the formula I according to one or more of Claims 1 to 16 as inhibitors of coagulation factor Xa.

19. Compounds of the formula I according to one or more of Claims 1 to 16 as inhibitors of coagulation factor VIIa.

20. Medicaments comprising at least one compound of the formula I according to one or more of Claims 1 to 16 and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.

21. Medicaments comprising at least one compound of the formula I according to one or more of Claims 1 to 16 and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and at least one further medicament active ingredient.

22. Use of compounds according to one or more of Claims 1 to 16 and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment of thromboses, myocardial infarction, arteriosclerosis, inflammation, apoplexy, angina pectoris, restenosis after angioplasty, claudicatio intermittens, migraine, tumours, tumour diseases and/or tumour metastases.

23. Set (kit) consisting of separate packs of
(a) an effective amount of a compound of the formula I according to one or more of Claims 1 to 16 and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios,
and
(b) an effective amount of a further medicament active ingredient.

24. Use of compounds of the formula I according to one or more of Claims 1 to 16 and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios,

for the preparation of a medicament for the treatment of thromboses, myocardial infarction, arteriosclerosis, inflammation, apoplexy, angina pectoris, restenosis after angioplasty, claudicatio intermittens, migraine, tumours, tumour diseases and/or tumour metastases, in combination with at least one further medicament active ingredient.